

Drug allergy: relationship between immunogenicity and clinical symptoms

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Side-effects of drugs are a major problem of drug therapy. Most side-effects can be related to the pharmacologic activity of the drug, but about 15% of all side-effects of drugs are thought to be immune mediated. The pathophysiology of drug-induced side-effects appears to be quite heterogeneous, as it may cause a wide variety of symptoms and mimic different diseases.

The current understanding of drug recognition by the immune system is based on the hapten model (1). Most drugs are organic chemicals with a molecular mass below 1000 kDa and are considered to be weakly immunogenic or nonimmunogenic. They can gain immunogenicity by covalent binding to proteins, forming hapten-carrier complexes. Examples of such drugs are β -lactams and cephalosporins (2). However, most drugs are, per se, not chemically reactive. Their metabolism may lead to reactive intermediates, which can covalently bind to carrier molecules. One well known example of such a drug is sulfamethoxazole (SMX), which is metabolized to chemically reactive intermediates such as hydroxylamine- and nitroso-SMX compounds (3). However, the immunogenicity of these intermediates has never been shown.

We recently elaborated a new model of drug recognition by *activated* T cells which supplements this hapten model. We term it "direct, metabolism-independent T-cell stimulation". It postulates drug binding to the MHC-peptide complex on the antigen-presenting cell (APC) and TCR in a way similar to drug binding to other pharmacologic receptors. Thus, noncovalent binding of the drug to a carrier protein is required for drug presentation. This concept relies

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on the finding that glutaraldehyde-fixed APC are still able to present drugs to drug-specific CD4+ and CD8+ T-cell clones (4). It also relies on the kinetics of drug recognition by specific T cells (5). This occurs within seconds to minutes, as shown by Ca²⁺ increase and TCR downregulation of drug-specific T-cell clones incubated with autologous APC and the drug. Such rapid kinetics is incompatible with an intermediate antigen-processing step, which requires over 4 h to lead to presentation on MHC molecules of processed peptides.

Has this new concept of drug presentation any implication for our understanding of drug-induced side-effects? I believe it does. The immune system is stimulated differently when drugs modify soluble proteins, cell-membrane structures, or even MHC molecules. As a consequence, different clinical manifestations may occur.

- 1) Most modifications of proteins by drugs seem to be ignored by the immune system. Most patients taking penicillins do not develop drug allergies. Only if additional signals are provided (probably in relation to localization of the hapten-modified protein to secondary lymphoid organs, provision of costimulatory signals by professional APC, or inflammatory signals ["danger"]) can an immune response evolve. This would explain why a generalized immune activation such as HIV or EBV infection is a cofactor for drug allergy.
- 2) Real haptens such as penicillins are able to cause many different forms of drug allergies, since haptens can modify

soluble proteins, cell membranes, and even MHC-peptide complexes directly (2). Depending on the predominant modification and immunogenicity of soluble or cell-membrane-associated proteins, different forms of drug allergy may develop. If soluble proteins are modified, *immunoglobulin (Ig)-mediated* disorders such as anaphylaxis or an immune complex disease may arise; if cell membranes are modified, blood cell dyscrasia may occur; and if MHC-peptide complexes are modified, *T-cell-mediated* exanthema, and probably other forms of drug allergy may arise (Table 1).

- 3) Most drugs are not haptens as they are chemically not able to bind covalently to proteins. If they cause allergies, it is attributable to drug metabolism able to generate reactive compounds (6). Then, both Ig and/or T-cell responses may develop against modified proteins or cells (i.e., hepatitis due to antibodies or T cells). This is presently the prevailing concept, but the experimental evidence supporting it is still scarce.
- 4) The most frequent clinical symptom of drug allergy is skin rash. It is clearly a T-cell-mediated reaction without evidence of formation of drug-specific Ig. It is often transient, and not always reproducible in provocation tests. T-cell clones from patients with exanthema recognize the drug in a direct way, without need of drug metabolism. Thus, skin rashes may well represent the main manifestation of this labile, metabolism-independent drug presentation by MHC-peptide complexes (7). These complexes are too labile to elicit Ig

Table 1. Covalent vs noncovalent drug binding may elicit different immune reactions: covalent binding can elicit many different reactions by T and B cells (immunoglobulins), while noncovalent drug binding may preferentially stimulate T-cell reactions

A) Covalent drug binding (i.e., β -lactams and cephalosporins):		
Soluble protein are modified:	cells are modified	MHC/peptides are modified either directly or via degradation of modified protein:
a) ignored by immune system	a) ignored by immune system	a) if no second signal (danger) occurs, immune system ignores it
b) Ig-mediated reactions such as IgE (anaphylaxis) or IgG (immune complex disease) may evolve in rare circumstances	b) hemolytic anemia or thrombocytopenia (Ig-mediated cell sequestration or lysis) may evolve in rare circumstances	b) if costimulation/lymph node localization, etc., occurs, immune reactions may develop, most frequently as contact dermatitis, maculopapular exanthema, bullous skin disease, hepatitis, etc.
B) Noncovalent drug binding: (SMX, lidocaine, etc.)		
soluble protein	cells	MHC/peptide
???	???	T-cell reactions:
		contact dermatitis, maculopapular exanthema, bullous skin disease, hepatitis, etc.

* Ig-mediated reaction seems to be possible, if drug modifies protein such that *preformed* autoantibodies react with protein (thrombocytopenia and hemolytic anemia).

responses, a fact which may explain the exclusive skin symptoms.

- 5) It is at present unclear whether drugs noncovalently bound to proteins can induce an IgG or an IgE response. Even if such a labile drug-protein complex were to be recognized by an Ig, it would be immediately dissociated in the process of protein uptake and degradation by APCs, a process required to stimulate T cells. Therefore, T-cell help – necessary for the Ig switch – may not be provided.

It would be an extreme exception if stimulation of B cells, which occurs by labile drug-protein complexes, and the distinct stimulation of T cells, which is due to direct drug binding to the MHC-peptide complex, should occur simultaneously.

- 6) There are peculiar situations where the covalently bound drug may alter antigen processing and elicit autoreactivity to a hidden peptide, or alter the structure of a protein, allowing binding of preformed Ig (6).

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